REMARKS

Applicants submit herewith a Supplemental Information Disclosure Statement listing recently issued (July 3, 2001) U.S. Patent No. 6,255,059, entitled, "Methods for Identifying G Protein Coupled Receptor Effectors."

I. Response to Restriction Requirement

In response to a restriction requirement mailed on June 24, 1999, Applicants provisionally elected Group I, claims 1- 18, 33-34, 39-40 without traverse. On November 13, 2000 and March 29, 2001, Applicants filed Amendments which canceled claims 1-18, inclusive, and added new claims 45-68. Claims 33, 34, 39, 40 and 45-68 are now pending and are subject to a new restriction.

In the Restriction Requirement, the Office has required Applicants to elect for examination one of what it considered to be 147 patentably distinct inventions. To summarize, the Office has indicated that each Location/Correlated Physiological Function in amended claims 33 and 39 are distinct and therefore subject to restriction.

Applicants provisionally elect herein "species" 116 encompassing "Location: ventromedial hypothalamus, Correlated with Physiological Function: food intake," and request that the non-elected "species" (1-115 and 117-147) be cancelled as indicated above. In making this election, Applicants take no legal position with respect to the view taken by the Office regarding the alleged distinctions between the 147 delineated "species." The Office has made this restriction based upon its view that a search of these "species" would create an undue burden on the Office. Applicants respectfully assert that only the Office is able to make this assumption. Nevertheless, Applicants are legally required to make an election in order to allow prosecution on the merits to continue.

Applicants reserve the right to prosecute the "species" encompassed by any of the non-elected Location/Correlated Physiological Function in future divisional applications.

Notwithstanding the foregoing, Applicants respectfully submit that the 147 "species" of Group I set forth by the Office are amenable to further grouping and that such further grouping would not impose a serious burden on the Office.

In order for an application to be properly required to be restricted, there must be a serious burden on the Examiner (*see*, MPEP §803). Indeed, the MPEP states that if the search and examination of an entire application can be made without serious burden, the Office must examine it on the merits, even though it includes claims to independent or distinct inventions. Applicants propose an alternative combination of the "species" identified by the Examiner. "Species" 106, 114, 115 and 116 in claims 33 and 39 are all related to food intake. Therefore, based upon the common correlated physiological function, *i.e.*, food intake, Applicants believe that no serious burden exists in examining these species as one group and therefore respectfully request consideration of this request.

II. The Lewis Declaration

A. Support for the Delineations in Claims 33 and 39

In the Restriction Requirement, the Office notes that "Although the Examiner will respond to the Applicants Amendments dated November 13, 2000 and March 29, 2001...Applicants are advised the Examiner can not find support for the Amended claims in the Specification." First, Applicants would like to thank the Examiner for the courtesy extended in reviewing these claims. Second, in specific response to the request by the Examiner, attention is drawn to the declaration of Michael Lewis, Ph.D. (hereinafter "Lewis Decla."), attached hereto as **Exhibit A**.

Dr. Lewis is currently the President of BioDiligence Partners, Inc., in West Chester, Pennsylvania. Dr. Lewis is a co-founder of and Scientific Consultant to Arena Pharmaceuticals, Inc., the owner of the present patent application. Dr. Lewis is also the co-founder of several other pharmaceutical companies, for example, Cephalon, Inc., West Chester, PA and Adolor Corporation, Malvern, PA. In 1973, Dr. Lewis received his B.A. in Psychology at George Washington University, Washington, DC; his M.A. in Psychology at Clark University in Worcester, MA; and his Ph.D. in Psychology at Clark University. In addition, Dr. Lewis has been a journal referee for several journals, including: Biochemical Pharmacology; Brain Research; Endocrine Journal; Experimental Neurology; Molecular and Cellular Neurosciences; Proceedings of the National Academy of Sciences; and Science. (*See*, Lewis Delca. ¶1).

Dr. Lewis is familiar with G protein-coupled receptors ("GPCR") and the significance of the expression pattern of a GPCR as it relates to a physiological function. (*See*, Lewis Delca. ¶3). Dr. Lewis is familiar with the procedures and requirements for obtaining and securing a patent, and is therefore familiar with the phrase "new matter." Dr. Lewis has reviewed and is familiar with the present application, the previous correspondence between Applicants and the Office, and the Restriction Requirement issued by the Office. (*See*, Lewis Delca. ¶4).

Dr. Lewis declares that the designated "Location" and "Correlated Physiological Function" of claims 33 and 39 were known and reported in several scientific references prior to the April 14, 1997 filing date and that, in his opinion, "these relationships...were established, understood and recognized prior to the filing date of the present patent application." (*See*, Lewis Delca. ¶5).

The relationships between the receptor Location and the Correlated Physiological Function provided in claims 33 and 39, are within the broad disclosure of the originally filed patent application. Dr. Lewis opines that these location-function relationships are "exemplary of the

broad disclosure" as disclosed in the patent application. As noted by Dr. Lewis, quoting from the application,

> "For example, scanning both diseased and normal tissue samples for the presence of a receptor now becomes more than an academic exercise or one which might be pursued along the path of identifying an endogenous ligand. Since, by definition, the endogenous ligand for an orphan receptor is not known, tissue scans can be conducted across a broad range of healthy and diseased tissues. Such tissue scans provide a preferred first step in associating a specific receptor, for which modulating compounds are now known, with a disease. The DNA sequence of a receptor may be used to make a probe for RT-PCR identification of the expression of the receptor in the tissue samples. The presence of the receptor in a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue strongly can be preferably utilized to identify a correlation with that disease. **Receptors can equally well be localized to regions of organs by this technique. Based upon the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced.**" Page 33, line 25 to page 34, line 12 (emphasis supplied); s*ee also*, Lewis Decla. ¶9).

Therefore, in Dr. Lewis' opinion, the Location/Correlated Physiological Function relationship in claims 33 and 39 are exemplary of the broad disclosure as originally filed. (*See*, Lewis Decla. ¶9).

Extensive cross referencing is made by Dr. Lewis for each of the 147 Location/Correlated Physiological Function of claims 33 and 39 based upon Goodman & Gilman's, The Pharmacological Basis of Therapeutics, 9th Edition (1996), Harrison's, Principle of Internal Medicine, 13th Edition, (1994), Daube, J. et al. Medical Nerosciences, An Approach to Anatomy, Pathology and Physiology by Systems and Level (1978), Kandel, E. et al., Essentials of Neural Science and Behavior (1995), Kandel, E. et al., Principles of Neural Science, 3rd Edition (1991), Isaaccon, R., The Limbic System, 2nd Edition (1982), and several journals listed in Appendix B of Dr. Lewis' declaration. (*See,* Lewis Decla. ¶5, *see also* Appendix B of Lewis Decla.). Dr. Lewis has attached to his declaration on Appendix B a chart listing the Location and Correlated

Physiological Function, as set forth in claims 33 and 39, together with the designated literature citation, all of which having publication dates prior to April 14, 1997 filing date.

Based upon review of the application as filed, the invention is focused on using receptors to directly identify candidate compounds based upon the compound efficacy of such compounds. Dr. Lewis opines that the "expression location of a receptor in a specific tissue can provide a scientist with the ability to determine the putative functional role of the receptor." (*See*, Lewis Decla. ¶6).

Dr. Lewis further declares that he has read the Declaration of Dr. Stanley J. Watson (the "Watson Declaration"), previously submitted and made of formal record in the application on November 13, 2000. Dr. Lewis notes that in the Watson Declaration, Dr. Watson discussed a GPCR designated by Arena with the code-name 18F, which was determined to be localized in an area of the brain, *e.g.*, hypothalamus, which is associated with feeding, and that a small molecule candidate compound directly identified by the method of the claimed invention decreased food consumption when administered to animals. (*See*, Lewis Decla. ¶8). Dr. Lewis declares that the designated location of the 18F GPCR therein, *i.e.,* ventromedial hypothalamus, identified as number 116 on Appendix B, is correlated with the physiological function of food intake. (*See*, Lewis Decla. ¶8). Upon applying the claimed invention to the 18F receptor, a candidate compound against the 18F receptor was directly identified as an inverse agonist, whereupon contacting the receptor with the directly identified candidate compound, the physiological function of the 18F receptor, food intake, was reduced. (*See*, Lewis Decla. ¶8). Dr. Lewis declares that the directly identified inverse agonist binds to the 18F receptor. Dr. Lewis further declares that he was informed and he believes that the 18F receptor is a receptor for which an endogenous ligand has not been identified. (*See*, Lewis Decla. ¶8).

B. Support for Expansion of the Restriction Required

As declared by Dr. Lewis, other areas of the hypothalamus are associated with feeding. (*See*, Lewis Decla. Appendix B). For example, Dr. Lewis was provided with in situ hybridization data of a receptor referred to as 19AL. Upon review of the data, Dr. Lewis declares that the data shows that 19AL is located in the lateral hypothalamus, which, as set forth in number 106 in claims 33 and 39, is correlated with feeding. (*See*, Lewis Decla. ¶10; *see also,* Appendix B, number 106). This physiological function is the same as that set forth in number 116 on Appendix B where the regions for both functions are the within the hypothalamus. (*See*, Lewis Decla. ¶10). *Inter alia*, this information, with due respect, provides additional support to the Office for expanding the restriction as requested above.

C. Compound Efficacy vs. "Binding Affinity"

According to the Specification, the phrase "compound efficacy" is defined as "a measurement of the ability of a compound to inhibit or stimulate the functional activity of the receptor, as opposed to receptor binding affinity." (*See*, Lewis Decla. ¶11; *see also*, page 18, lines 3 to 4 of the Specification). Dr. Lewis declares that the claimed invention does not rely upon the mere binding of the candidate compound to the receptor's endogenous ligand binding site (binding affinity). (*See*, Lewis Decla. ¶11). A compound directly identified by the claimed invention not only must bind to a receptor, but in Dr. Lewis' scientific opinion, the compound must inhibit or stimulate the function of a receptor. (*See*, Lewis Decla. ¶11). Further, based upon Dr. Lewis' education and work related experiences, Dr. Lewis opines that the compound efficacy is much more relevant in terms of the activity of a compound on the receptor than measuring the affinity for which a compound binds to a receptor's endogenous ligand binding site. (*See*, Lewis Decla. ¶11). Stated

differently, a compound that has a strong affinity for a receptor may have little or no effect on the physiological function associated with the receptor, but as disclosed in the Specification, an "inverse agonist" or an "agonist" identified specifically defines the functional effect such a compound will have on the receptor. (*See*, Lewis Decla. ¶11). Dr. Lewis declares that the binding affinity of a compound for a receptor only defines the ability of the compound to bind to the receptor at the endogenous ligand binding site. (*See*, Lewis Decla. ¶11).

To clarify, Dr. Lewis declares that, in his scientific opinion, knowing the binding affinity will not define the functional activity of a compound, which is "much more significant" in identifying candidate compounds to a receptor. (*See*, Lewis Decla. ¶12).

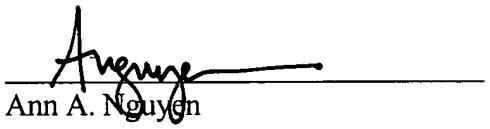
D. Claims 33 and 39 As Amended And "Real World" Utility

In addition to the extensive scientific opinions provided in the Watson Declaration regarding the real world utility of the invention disclosed by the Applicants, Dr. Lewis also provides his scientific opinion on this issue. Claims 33 and 39 provide a step in which the candidate compound is placed in contact with a mammal comprising the receptor and confirming the increase or decrease of a physiological function against which the candidate compound was directly identified. In Dr. Lewis's opinion, an orphan receptor processed through the claimed invention is less of a "pure" orphan receptor because the candidate compound identified will bind to the receptor and alter a physiological function associated with that receptor. (*See*, Lewis Decla. ¶13). Dr. Lewis declares that although the candidate compound identified is not the endogenous ligand, in Dr. Lewis' scientific opinion the compound directly identified by the application of the claimed invention has a real world use because the compound will impact a defined physiological function in a mammal. (*See*, Lewis Decla. ¶13).

III. Conclusion

Applicants respectfully submit that the foregoing arguments and amendments place this application in condition for allowance. Applicants invite the Examiner to contact the undersigned to clarify any unresolved issues raised by this response. The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicants respectfully request early notification of the same.

Respectfully submitted,



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Attachments:

"Version with markings to show changes made"

VERSION WITH MARKINGS TO SHOW CHANGES MADE

33 (Amended Four Times). A method for directly identifying a non-endogenous candidate compound as a compound having activity selected from the group consisting of inverse agonist activity and agonist activity to an endogenous G protein coupled cell surface receptor, wherein a location of expression of said receptor has been identified from a mammalian tissue source and has been correlated with at least one physiological function in a mammal, comprising the steps of:

(a) selecting an endogenous G protein coupled cell surface receptor, wherein the endogenous ligand for said receptor has not been identified;

(b) determining the location of expression of said receptor in a mammalian tissue source and correlating the expression location of said receptor with at least one mammalian physiological function of interest, wherein said location and said correlated physiological function are selected from the group consisting essentially of:

Location:		Correlated Physiological Function:
1. gastrointestinal tract smooth muscle		1. motility of stomach and intestines
2. gastrointestinal tract ganglionic nerve fibers		2. motility of stomach and intestines
3. urinary tract smooth muscle		3. ureter function and urinary bladder function
4. salivary gland		4. salivary secretion
5. alpha cells of the pancreas		5. secretion of glucagon
6. beta cells of the pancreas		6. secretion of insulin
7. uterine smooth muscle		7. uterine contraction
8. heart muscle		8. contractility of heart muscle
9. vascular smooth muscle		9. contractility of smooth muscle
10. adipocytes		10. lipolysis
11. platelets		11. platelet aggregation in response to blood vessel injury
12. skeletal neuromuscular junction		12. skeletal muscle contractility
13. bronchial smooth muscle		13. respiration
14. nasal mucosal blood vessels		14. mucosa volume
15. trigone muscle of bladder and urethra		15. urinary outflow
16. chondrocytes		16. cartilage formation
17. ciliary body of the eye		17. aqueous humor production
18. thyroid		18. thyroid hormone secretion
19. mast cells		19. immediate hypersensitivity reactions
20. basophils		20. immediate hypersensitivity reactions
21. osteoblasts		21. bone remodeling
22. osteoclasts		22. bone remodeling
23. brain capillary endothelial cells		23. permeability of blood-brain barrier
24. T cells		24. immune response
25. B cells		25. immune response

26. kidney proximal tubular epithelial cells	26. organic acids exchange
27. neutrophils	27. immune response
28. eosinophils	28. immune response
29. monocytes	29. immune response
30. kidney late distal tubule	30. organic bases exchange
31. collecting duct principal cells	31. organic bases exchange
32. kidney granular juxtaglomerular cells	32. secretion of renin
33. peripheral postganglionic adrenergic neurons	33. sympathetic function
34. hepatocytes	34. synthesis of cholesterol and lipoprotein
35. gastrointestinal parietal cells	35. secretion of stomach acid
36. gastrointestinal superficial epithelial cells	36. secretion of cytoprotective factors, mucus and bicarbonate
37. epidermal cells	37. skin maintenance
38. bone marrow stem cells	38. erythropoesis production
39. angle structures of the eye	39. aqueous humor outflow
40. uveoscleral structures of eye	40. aqueous humor outflow
41. suprachiasmatic nucleus	41. circadian rhythm
42. baroreceptors	42. blood pressure
43. basal ganglia	43. movement control
44. periaqueductal grey and dorsal horn of spinal cord	44. nociception
45. area postrema	45. vomiting
46. thalamus	46. sensorimotor processing and arousal
47. sensorimotor cerebral cortex	47. sensorimotor processing
48. spinal cord motor neurons	48. motor function control
49. dorsal root ganglion neurons	49. sensory information transmission
50. oligodendrocytes	50. neuron myelin sheath production
51. nucleus basalis	51. cognition and memory
52. nucleus accumbens	52. addictive cravings
53. lateral reticular formation of medulla	53. vomiting
54. hypothalamic neurons containing growth hormone releasing factor (GHRH)	54. secretion of GHRH
55. hypothalamic neurons containing somatostatin	55. secretion of somatostatin
56. hypothalamic neurons containing thyrotropin-releasing hormone (TRH)	56. secretion of TRH
57. hypothalamic neurons containing gonadotropin releasing hormone (GnRH)	57. secretion of GnRH
58. hypothalamic neurons containing corticotropin releasing factor (CRF)	58. secretion of CRF
59. anterior pituitary somatotropes	59. secretion of growth hormone
60. anterior pituitary lactotropes	60. secretion of prolactin
61. anterior pituitary gonadotropes	61. secretion of luteinizing hormone
62. anterior pituitary gonadotropes	62. secretion of follicle stimulating hormone
63. anterior pituitary corticotropes	63. secretion of adrenocorticotropic hormone

64. leydig cells of the testes		64. secretion of testosterone
65. sertoli cells of the testes		65. spermatogenesis
66. granulosa cells of the ovary		66. synthesis of estrogen
67. theca cells of the ovary		67. synthesis of estrogen
68. synovium		68. joint function
69. amygdala		69. modulation of emotion
70. pineal gland		70. regulation of circadian rhythm
71. nucleus of the solitary tract		71. cardiovascular regulation
72. caudal ventrolateral medulla		72. cardiovascular regulation
73. rostral ventrolateral medulla		73. vasopressor activity
74. parabrachial nucleus		74. taste aversion response and nociceptive response
75. entorhinal cortex		75. cognition
76. pyriform cortex		76. cognition
77. temporal cortex		77. memory acquisition
78. frontal cortex		78. regulation of emotional response and memory acquisition
79. parietal cortex		79. visual acuity, touch perception, and voluntary movement
80. occipital cortex		80. visual acuity
81. hippocampus		81. learning and memory
82. dentate gyrus		82. learning and memory
83. midbrain reticular formation		83. arousal
84. supraoptic nucleus of the hypothalamus		84. reproductive functions
85. magnocellular of the hypothalamus		85. modulation of stress, blood pressure and lactation
86. parvocellular neurons of the hypothalamus		86. metabolism
87. arcuate nucleus of the hypothalamus		87. release of pituitary hormones
88. trigeminal area		88. cerebral vessel dilation and blood pressure
89. cerebral blood vessels		89. cerebral vessel dilation
90. brain stem		90. breathing, heart rate, startle responses, sweating, blood pressure, digestion and body temperature
91. ventral lamina terminalis		91. blood pressure
92. vagus nerve		92. blood pressure and heart rate
93. nucleus of the solitary tract		93. blood pressure
94. adrenal medulla		94. catecholamine response to stress
95. adrenal cortex		95. stress-induced corticosterone release
96. locus coeruleus		96. arousal and response to stress
97. substantia nigra		97. control of body movement
98. ventral tegmental area		98. control of body movement
99. olfactory bulb		99. odor perception
100. median eminence of hypothalamus		100. pituitary function
101. raphe nuclei		101. sleep and arousal
102. habenula		102. sexual activity
103. cerebellum		103. control of body movement

104. posterior hypothalamus	104. intestinal motility and blood pressure
105. dorsal medulla	105. blood pressure
106. lateral hypothalamus	106. food intake and stomach acid secretion
107. rostral hypothalamus	107. heart rate
108. pontine-medullary reticular formation	108. respiration and heart rate
109. medulla	109. respiration and heart rate
110. mesencephalon	110. heart rate
111. ventral hypothalamus	111. response to stress
112. paraventricular nucleus of hypothalamus	112. response to stress
113. preoptic area of hypothalamus	113. sexual activity
114. mammillary region	114. food intake
115. perifornical area of hypothalamus	115. food intake
116. ventromedial hypothalamus	116. food intake
117. pons/reticular formation	117. arousal and wakefulness
118. septum	118. emotional control
119. pedunculopontine tegmental nucleus	119. arousal
120. astrocytes	120. neuronal metabolism
121. microglia	121. response to neuronal injury
122. choroid plexus	122. production of cerebrospinal fluid
123. Schwann cells	123. myelination of peripheral nerves
124. endoneurium	124. production of connective tissue nerve sheath
125. lateral spinothalamic pathway	125. response to pain and temperature stimuli
126. ventral spinothalamic pathway	126. touch sensation
127. dorsal column-medial lemniscal pathway	127. touch sensation
128. free nerve endings	128. response to pain and temperature
129. hair follicle endings	129. touch sensation
130. Krause's end-bulb	130. temperature sensation
131. Meissner's corpuscles	131. touch-pressure sensation
132. Merkel's disk	132. touch-pressure sensation
133. Pacinian corpuscle	133. touch-pressure sensation
134. Ruffini's corpuscle	134. temperature sensation
135. retina	135. visual acuity
136. parathyroid gland	136. calcium balance
137. placenta	137. placental activity
138. skeletal muscle fibers	138. muscle contraction
139. copora cavernosum	139. genital vasodilation
140. corticospinal tract	140. movement control
141. motor cerebral cortex	141. movement control
142. postganglionic neurons	142. control of blood pressure and adrenal activity
143. intramural ganglion	143. distal colon peristalsis
144. hypogastric plexus	144. control of urethral and anal sphincters
145. pelvic plexus	145. genital vasodilatation and penile erection

146. vesical plexus	146. urinary bladder control
147. celiac plexus	147. intestinal peristolisis
Location:	Correlated Physiological Function:
116. ventromedial hypothalamus	116. food intake

(c) subjecting said receptor to constitutive receptor activation to establish a non-endogenous constitutively activated G protein coupled cell surface receptor;

(d) contacting a non-endogenous candidate compound with said non-endogenous constitutively activated G protein coupled cell surface receptor of step (c);

(e) determining, by measurement of the compound efficacy at said contacted receptor, whether said non-endogenous candidate compound has inverse agonist activity or agonist activity to said receptor of step (c); and

(f) directly identifying a non-endogenous candidate compound of step (e) having inverse agonist activity as an inverse agonist to said receptor of step (c), or having agonist activity as an agonist to said receptor of step (c);

(g) selecting an inverse agonist to reduce a selected physiological function of step (b) correlated with the tissue-expression location for said receptor of step (a), or selecting an agonist to enhance a selected physiological function of step (b) correlated with the tissue-expression location for said receptor of step (a); and

(h) contacting said inverse agonist with a mammal comprising said receptor of step (a) and confirming that said inverse agonist reduces said selected physiological function, or contacting said agonist with a mammal comprising said receptor of step (a) and confirming that said agonist enhances said selected physiological function

wherein said directly identified non-endogenous candidate compound of step (f) was not, prior to such direct identification, indirectly identified as an agonist or antagonist to said endogenous G protein coupled cell surface receptor.

Claim 39 (Amended Four Times) A method for directly identifying a non-endogenous candidate compound as a compound having activity selected from the group consisting of inverse agonist activity and agonist activity to an endogenous constitutively activated G protein coupled cell surface receptor, wherein a location of expression of said receptor has been identified from a mammalian tissue source and has been correlated with at least one physiological function in a mammal, comprising the steps of:

(a) selecting an endogenous constitutively activated G protein coupled cell surface receptor, wherein the ligand for said receptor has not been identified;

(b) determining the location of expression of said receptor in a mammalian tissue source and correlating the expression location of said receptor with at least one mammalian physiological function of interest, wherein said location and said correlated physiological function are selected from group consisting essentially of:

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73. rostral ventrolateral medulla		73. vasopressor activity
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110. mesencephalon		110. heart rate
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115. perifornical area of hypothalamus		115. food intake
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123. Schwann cells		123. myelination of peripheral nerves
124. endoneurium		124. production of connective tissue nerve sheath
125. lateral spinothalamic pathway		125. response to pain and temperature stimuli
126. ventral spinothalamic pathway		126. touch sensation
127. dorsal column-medial lemniscal pathway		127. touch sensation
128. free nerve endings		128. response to pain and temperature
129. hair follicle endings		129. touch sensation
130. Krause's end-bulb		130. temperature sensation
131. Meissner's corpuscles		131. touch-pressure sensation
132. Merkel's disk		132. touch-pressure sensation
133. Pacinian corpuscle		133. touch-pressure sensation
134. Ruffini's corpuscle		134. temperature sensation
135. retina		135. visual acuity
136. parathyroid gland		136. calcium balance
137. placenta		137. placental activity
138. skeletal muscle fibers		138. muscle contraction
139. copora cavernosum		139. genital vasodilation
140. corticospinal tract		140. movement control
141. motor cerebral cortex		141. movement control
142. postganglionic neurons		142. control of blood pressure and adrenal activity
143. intramural ganglion		143. distal colon peristalsis
144. hypogastric plexus		144. control of urethral and anal sphincters
145. pelvic plexus		145. genital vasodilatation and penile erection
146. vesical plexus		146. urinary bladder control
147. celiac plexus		147. intestinal peristolisis

(c) contacting a non-endogenous candidate compound with said endogenous constitutively activated G protein coupled cell surface receptor of step (a);

(d) determining, by measurement of the compound efficacy at said contacted receptor, whether said non-endogenous candidate compound has inverse agonist activity or agonist activity to said receptor of step (a); and

(e) directly identifying a non-endogenous candidate compound of step (d) having inverse agonist activity as an inverse agonist to said receptor of step (a), or having agonist activity as an agonist to said receptor of step (a);

(f) selecting an inverse agonist to reduce a selected physiological function of step (b) correlated with the tissue-expression location for said receptor of step (a), or selecting an